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Abstract: BACKGROUND/AIMS: Excessive daytime sleepiness (EDS) is frequent in patients with Parkinson's disease (PD). Occasionally, EDS in PD exhibits narcolepsy-like features. We aimed to assess characteristics and determinants of EDS in consecutive patients with PD. METHODS: Thirty consecutive patients with PD underwent a detailed clinical examination. EDS was assessed using the Epworth Sleepiness Scale (ESS) and Multiple Sleep Latency Test (MSLT). Sleep was assessed using video-polysomnography. Cerebrospinal fluid (CSF) hypocretin-1 levels were obtained in 3 patients. RESULTS: ESS was >10 in 17 patients (57%). Mean sleep latency (MSL) on MSLT was <5 min in 11 patients (37%). There was a significant negative correlation between ESS and MSL. None of the 11 patients with MSL <5 min showed a sleep onset REM (SOREM) episode. Patients with EDS had higher dopamine agonists/levodopa equivalent doses, higher apnea/hypopnea index and exhibited wearing-off symptoms more often. Hypocretin-1 was normal in 3 patients tested. CONCLUSION: EDS, which can sometimes be severe, is common in PD patients even in the absence of SOREM and detectable CSF-hypocretin deficiency. In PD, EDS is a multifaceted phenomenon, the determinants of which include severity of PD, wearing-off symptoms, dosage of antiparkinsonian drugs and sleep-disordered breathing.

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Excessive Daytime Sleepiness in Parkinson's Disease: Characteristics and Determinants

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Key Words
Excessive daytime sleepiness · Sleep onset REM · Parkinson's disease · Multiple sleep latency test

Abstract
Background/Aims: Excessive daytime sleepiness (EDS) is frequent in patients with Parkinson's disease (PD). Occasionally, EDS in PD exhibits narcolepsy-like features. We aimed to assess characteristics and determinants of EDS in consecutive patients with PD. ***Methods:*** Thirty consecutive patients with PD underwent a detailed clinical examination. EDS was assessed using the Epworth Sleepiness Scale (ESS) and Multiple Sleep Latency Test (MSLT). Sleep was assessed using video-polysomnography. Cerebrospinal fluid (CSF) hypocretin-1 levels were obtained in 3 patients. ***Results:*** ESS was >10 in 17 patients (57%). Mean sleep latency (MSL) on MSLT was <5 min in 11 patients (37%). There was a significant negative correlation between ESS and MSL. None of the 11 patients with MSL <5 min showed a sleep onset REM (SOREM) episode. Patients with EDS had higher dopamine agonists/levodopa equivalent doses, higher apnea/hypopnea index and exhibited wearing-off symptoms more often. Hypocretin-1 was normal in 3 patients tested. ***Conclusion:*** EDS, which can sometimes be severe, is common in PD patients even in the absence of SOREM and detectable CSF-hypocretin deficiency. In PD, EDS is a multifaceted phenomenon, the determinants of which include severity of PD, wearing-off symptoms, dosage of antiparkinsonian drugs and sleep-disordered breathing.

Introduction

Excessive daytime sleepiness (EDS) is common, although often underestimated in patients with Parkinson's disease (PD). An Epworth Sleepiness Scale score (ESS) above 10, indicating subjective EDS, has been reported in up to 50% of patients with PD [1]. Frucht et al. [2] and other authors have reported sudden sleep episodes ('sleep attacks') causing driving accidents in PD patients taking non-ergot dopamine agonists. Severe EDS, defined as mean sleep latency (MSL) on the Multiple Sleep Latency Test (MSLT) <5 min, has been reported in about 20% of unselected patients with PD [3, 4] and in up to 50% of PD patients with EDS [5]. Data on the frequency of sleep onset REM (SOREM) have been variable. SOREM was found in 29–39% of PD patients with EDS [5, 6] and in up to 70% of PD patients with hallucinations [7]. SOREM was also observed in a case of juvenile PD [8] and in 20–28% of unselected PD patients [4, 9, 10]. Others have reported a less frequent occurrence of SOREM in PD and other forms of parkinsonism [11].

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Table 1. Main demographic and clinical characteristics of 30 patients with Parkinson's disease included in the study and 194 patients with PD, seen in the outpatient's clinic for movement disorders over 2 years

	Patients with assessment of sleep and sleepiness (n = 30)	Outpatients (n = 194)	p
Age, years	65 ± 10 (45–78)	67 ± 10 (36–89)	NS
Disease duration, years	8.2 ± 6.6 (0–29)	8.5 ± 6.6 (0–29)	NS
UPDRS III	25 ± 10 (7–44)	24 ± 12 (4–74)	NS
Hoehn and Yahr Stage	2.5 ± 0.9 (1–4)	2.5 ± 1 (1–4)	NS
Dopamine agonist equivalent dose, mg	205 ± 230 (0–700)	211 ± 218 (0–1,000)	NS
Levodopa equivalent dose, mg	651 ± 531 (0–2,011)	632 ± 436 (0–2,140)	NS

Values are means ± SD (range). UPDRS III = Unified Parkinson's Disease Rating Scale part III.

Subjective (as assessed by ESS) and objective (as assessed by MSLT) EDS in PD was systematically examined in 8 studies. In 6 studies, consecutive unselected PD patients were included [3, 4, 9, 10, 12, 13]. In 2 studies, only PD patients referred for sleepiness or with ESS >10 were examined [5, 6]. Various factors including age [14, 15], gender [1, 16], dopaminergic treatment [9, 17, 18], severity of PD [18, 19] and night-time sleep disturbances [5, 12] have been discussed as causes of EDS in PD. Neurons producing hypocretin (a hypothalamic protein involved in sleep-wake regulation, food intake and reward mechanism) were recently shown to be reduced in PD [20, 21]. Low cerebrospinal fluid (CSF) hypocretin-1 levels were found in 1 study assessing severe idiopathic PD patients [22], but were not confirmed in 3 subsequent studies [11, 23, 24].

The aim of this study was to assess, by means of a multimodal approach, the characteristics and potential determinants of EDS in a nonselected population of PD patients.

Patients and Methods

Daytime sleepiness and night-time sleep was assessed in 30 unselected consecutive patients (24 men; mean age 65 ± 10 years SD) with idiopathic PD, diagnosed according to the UK PD Brain Bank criteria [25]. The study was approved by the local ethics committee and all patients gave informed written consent prior to the study. Based on their characteristics, these patients were similar to 194 PD patients seen in our outpatient clinic for movement disorders over a 2-year period (2005–2006; table 1).

The mean disease duration at the time of the polysomnography/MSLT was 8.2 years (SD 6.6 years), ranging from 1 month to 29 years. The mean Unified Parkinson's Disease Rating Scale part III (UPDRS III, motor score) was 25 (SD 10, range 7–44) in 'on' condition and the mean Hoehn and Yahr (HY) stage was 2.5 (SD 0.9, range 1–4). Fourteen patients had advanced PD (HY ≥3), of whom 4 patients suffered from severe PD (HY = 4). Sixteen of the 30 patients reported a depressed mood, 16 patients had memory difficulties, 11 had wearing-off symptoms, 8 had peak-dose dyskinesia and 8 experienced visual hallucinations. Antiparkinsonian drugs included levodopa (n = 22), non-ergot (pramipexole and ropinirole) and ergot (pergolide, cabergoline) derivatives (n = 16), apomorphine (n = 1), COMT inhibitors (n = 5), amantadine (n = 5), and anticholinergics (n = 3). The mean levodopa equivalent dose was 651 mg (SD 531, range 0–2,011). Six patients were taking sleeping pills and 10 patients were taking antidepressants.

Subjective sleepiness was assessed using ESS. All patients underwent standard nocturnal video-polysomnography consisting of 4 channel EEGs (C3/A2, C4/A1, O1/A2, O2/A1), left and right electro-oculography, submental electromyography, electrocardiography, respiratory flow (using a nasal cannula) and effort (using Medcare XactTrace respiratory inductive plethysmography technology belts), pulse oximetry, and left and right anterior tibialis electromyography. All recordings were done on Medcare Somnologica Studio. Sleep stages, periodic limb movements and arousals were scored manually according to international criteria [26–28]. Apnea and hypopnea were scored according to the recommendations of the American Academy of Sleep Medicine [29], but differing in that a desaturation of 4% instead of 3% was needed when the amplitude decrease did not reach 50%. Sleep onset was defined as the first epoch of either NREM 2 or REM sleep.

On the day following the nocturnal recording, standard MSLT [30] was performed, starting 2 hours after waking up. For each patient, 4 (n = 20) or 5 (n = 5) naps, each with a duration of 20 min in 2-hour intervals were recorded. Sleep onset was defined as the first epoch of any sleep stage, including stage 1. The naps were terminated after 20 min. After each nap, the patients were asked to estimate if they had fallen asleep or not.

The hypocretin level in CSF was measured in 3 patients.

Statistical analysis was performed using SPSS 15 software. χ^2 tests, t tests, repeated measures ANOVA and Mann-Whitney tests were used to analyze categorical and continuous variables. Pearson's correlation was used to measure the degree of association between MSL, ESS, subjectively reported sleep duration, night-time sleep parameters, levodopa equivalent dose, disease severity and duration. The significance level was set at $p < 0.05$.

Results

The data on ESS, polysomnography and MSLT of the entire population are presented in table 2.

Sleep-disordered breathing [apnea/hypopnea index (AHI) >10/h] was found in 10 patients (33% of the entire population), and was severe (AHI >30) in 5 of them. In 2 of these patients, CPAP treatment was previously attempted but not tolerated. In 3 patients, the apneas were mostly of central origin.

Periodic limb movements in sleep (>10/h) was found in 5 (17% of the entire population).

Subjective Sleepiness (ESS)

Seventeen patients (57% of the entire population) reported subjective EDS (ESS >10). In 7 patients (23%), EDS was severe and 'narcolepsy like' (ESS ≥14) [31].

Patients with EDS had a significantly higher dopamine agonist dose, higher levodopa equivalent dose, shorter night-time sleep latency and shorter MSL on MSLT than patients without EDS (table 3). Additionally, a trend towards a lower nocturnal percentage of REM sleep was observed. No significant differences were observed regarding age, gender, disease duration and severity (as expressed by UPDRS III and HY stage), or other polysomnographic sleep parameters. ESS did not correlate with the subjectively reported sleep duration at home.

Objective Sleepiness (MSL on MSLT)

The MSL on MSLT was 9.2 min (SD 6.4, range 0.3–20). Eleven patients (37%) had severe objective EDS, which is a MSL ≤5 min. In 53 of 125 nap opportunities (42%), the sleep latency was ≤5 min. Sixteen patients had at least 1 nap with a sleep latency ≤5 min. From the 11 patients with a MSL ≤5 min, in 7 patients, all naps had a sleep latency ≤5 min (4 of 4 naps in 6 patients, and 5 of 5 naps in 1 patient); in 3 patients, 3 out of 4 naps were with a sleep latency ≤5 min; and in 1 patient, 2 out of 4 naps were with a sleep latency of ≤5 min. Repeated measures ANOVA showed no significant difference between the mean duration of the naps, regardless of the time of the test (data sphericity was not violated, $p = 0.75$, $F_3 = 0.406$). The distribution of naps with sleep latency ≤5 min was as follows: 15/30 in the 1st nap, 10/30 in the 2nd nap, and 13/30 in both the 3rd and 4th nap. These frequencies were not significantly different (Pearson χ^2, $p = 0.63$). There were 5 patients with a 5th nap (in one of them sleep latency was ≤5 min) and the mean duration of the 5th nap did not differ from the first 4 naps (table 4).

Table 2. ESS, polysomnographic and MSLT data in 30 consecutive patients with PD

	Mean ± SD	Range
ESS score	10 ± 5	0–17
Subjective night-time sleep duration, h	6.5 ± 1.9	2–10
Total sleep time, min	314 ± 66	165–421
Nocturnal sleep latency in PSG, min	35 ± 46	2–227
Sleep efficiency, %	79 ± 16	28–98
REM latency, min	118 ± 87	26–378
NREM 1, %	12 ± 5	1–24
NREM 2, %	43.4 ± 14	12–81
Slow wave sleep, %	12 ± 9	0.1–33
REM, %	12 ± 7	0–27
AHI	15 ± 21	0–63
PLMS index	10 ± 22	0–81
Mean sleep latency in MSLT, min	9.2 ± 6.4	0.3–20

PSG = Polysomnography; AHI = apnea/hypopnea index; PLMS = periodic leg movement in sleep.

Table 3. PD patients with (ESS >10) and without subjective EDS

	ESS >10 (n = 17)	ESS ≤10 (n = 13)	p
Nocturnal sleep latency, min	19 ± 28	57 ± 56	0.021
REM, %	10 ± 6	14 ± 7	0.087
Mean sleep latency in MSLT, min	6 ± 5	13 ± 6	0.005
Dopamine agonist equivalent dose, mg	310 ± 226	68 ± 155	0.003
Levodopa equivalent dose, mg	836 ± 426	408 ± 573	0.026

Only statistically significant results and trends are shown.

Table 4. Mean duration of the naps and number of naps with a sleep latency ≤5 min depending on the time of the test

Nap No.	Patients, n	Mean ± SD	Naps with a SL ≤5 min, n
Nap 1	30	9.1 ± 7.5	15
Nap 2	30	9.6 ± 7.2	10
Nap 3	30	8.5 ± 7.1	13
Nap 4	30	8.9 ± 7.2	13
Nap 5	5	8.1 ± 6.4	1

Repeated measures ANOVA $p = 0.75$, $F_3 = 0.406$; χ^2 $p = 0.63$. SL = Sleep latency. Because of the small number of patients with a 5th nap these data were not included in the repeated measures ANOVA analysis and the χ^2 statistics.

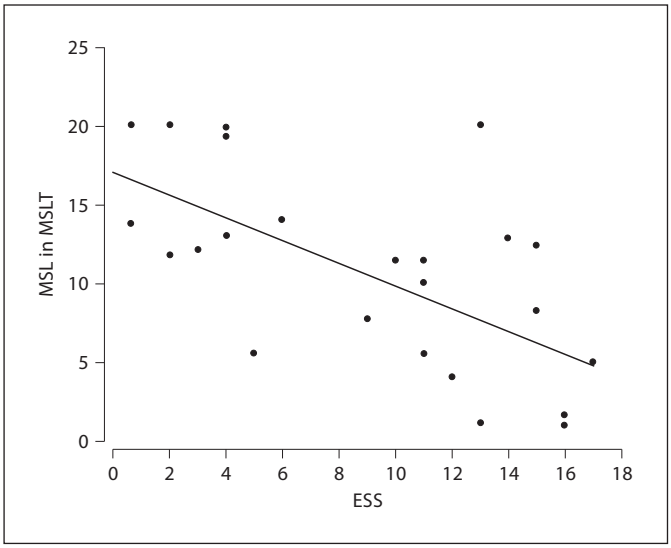

Fig. 1. Correlation between ESS and MSL in MSLT ($r = -0.65$, $p < 0.001$).

Table 5. PD patients with (MSL ≤5 min) and without severe objective EDS

	MSL ≤5 (n = 11)	MSL >5 (n = 19)	p
ESS score	14 ± 2	8 ± 5	0.001
Nocturnal sleep latency in PSG, min	11 ± 9	50 ± 53	0.001
AHI	24 ± 26	9 ± 15	0.026
Dopamine agonist equivalent dose mg	306 ± 216	146 ± 222	0.066

Only significant results and trends are shown.
MSL = Mean sleep latency on MSLT; PSG = polysomnography.

A significant correlation between the subjectively reported sleep duration at home and MSL was observed only in the patients with ESS >10 ($r = 0.531$, $p = 0.034$).

A highly significant negative correlation was found between ESS and the MSL in MSLT ($r = -0.65$, $p < 0.001$; fig. 1).

Patients with MSL <5 min had significantly shorter nocturnal sleep latency, higher ESS scores and a higher AHI when compared to patients with MSL >5 min (table 5). A trend towards a higher dopamine agonist equivalent dose was also observed. No significant differences were observed regarding age, gender, disease duration and severity (as expressed by UPDRS III and HY stage), other polysomnographic sleep parameters, or overall levodopa equivalent dose.

In 15 patients (50%), a sleep-wake misperception was present: 10 patients (33%) did not realize they fell asleep (sleep-state misperception) in at least 1 nap, and the other 5 (17%) thought they fell asleep although they did not (wake-state misperception). Patients with sleep-state misperception did not differ from the rest of the population studied regarding ESS, MSL, night-time parameters, demographic characteristics, disease duration or severity. Patients with wake-state misperception had significantly longer MSL (17.2 ± 3.8 min) in comparison to the rest of the population (7.5 ± 5.6 min, $p < 0.001$). Five patients with ESS >10 had normal MSL in MSLT (>8 min) and only 1 patient with short MSL (5.6 min) had a normal ESS (5/24 points).

No correlation was observed between ESS or MSL and age.

SOREM was not recorded in any test in any of the 11 patients with MSL ≤5 min who slept for 15 min after sleep onset. As the naps were terminated after 20 min, SOREM in the rest of the patients is not reported.

No significant differences regarding ESS, MSL and night-time parameters were observed between patients with advanced/severe (HY ≥3, n = 14) and beginning/light (HY <3, n = 16) PD.

Eight patients reported hallucinations. Patients with hallucinations had significantly higher UPDRS III scores (33 ± 9 vs. 21 ± 9, $p = 0.004$), especially when tremor-related points were excluded (33 ± 9 vs. 19 ± 10, $p = 0.002$), had a higher HY stage (3.1 ± 0.8 vs. 2.3 ± 0.9, $p = 0.033$) and less REM sleep (6.2 ± 7.5 vs. 13.7 ± 5.6%, $p = 0.006$). They tended to be objectively sleepier during the day than the patients without hallucinations (MSL in patients with hallucinations 5.8 ± 5.9 min, without hallucinations 10.4 ± 6.3 min, mean ± SD, $p = 0.081$) and fall asleep faster at night (night-time sleep latency in patients with hallucinations 13.9 ± 11.1 min, without hallucinations 43.3 ± 51.5 min, mean ± SD, $p = 0.07$).

Patients with wearing-off symptoms (n = 11) had lower MSL (5.9 ± 5.8 vs. 11 ± 6.1, $p < 0.031$), a higher HY stage (2.9 ± 0.9 vs. 2.2 ± 0.9, $p = 0.047$), longer therapy duration (9.9 ± 5.2 vs. 4.7 ± 6.9 years, $p = 0.04$), a higher dopamine agonist equivalent dose (330 ± 256 vs. 132 ± 183 mg, $p = 0.02$) and a higher levodopa equivalent dose (1,034 ± 457 vs. 429 ± 445 mg, $p = 0.001$) when compared to patients without wearing-off symptoms.

Both ESS and MSL correlated significantly with nocturnal sleep latency, dopamine agonist equivalent dose

Table 6. Significant associations with subjective (ESS) or objective [mean sleep latency (MSL) in MSLT] measures of EDS

	ESS		MSL	
	r	p	r	p
Hoehn and Yahr stage	0.074	0.698	–0.063	0.741
UPDRS III	–0.082	0.673	0.091	0.640
Total sleep time	0.067	0.725	–0.150	0.427
Sleep efficiency in PSG	–0.205	0.277	0.052	0.785
Sleep latency, min	–0.599	<0.001	0.581	0.001
REM, %	–0.345	0.062	0.393	0.032
AHI	0.392	0.032	–0.347	0.042
Dopamine agonist equivalent dose, mg	0.562	0.001	–0.484	0.007
Levodopa equivalent dose, mg	0.392	0.032	–0.348	0.059

and AHI. ESS also correlated with levodopa equivalent dose and MSL to the percentage of REM sleep. No correlation was found with other nocturnal sleep parameters or disturbances, motor functioning (as expressed by UPDRS III in 'on' condition), disease duration or severity (as expressed by HY stage; table 6).

CSF Hypocretin-1 Levels

Hypocretin-1 level in CSF was measured in 3 patients and was in the normal range in all of them (low <110 pg/ml, intermediate 110–200 pg/ml, normal >200 pg/ml) [32].

The 1st patient denied having hallucinations, his ESS was 11, his MSL was 5.5 min and CSF hypocretin-1 levels were 454 pg/ml. The 2nd patient was a woman who repeatedly complained of EDS (ESS 13), but no sleep was registered in MSLT. She did not report hallucinations and her hypocretin level was normal at 519 pg/ml. The other patient also complained of EDS (ESS 12), had MSL of 5 min, and no SOREM was registered. He did not report hallucinations and his hypocretin in CSF was 260 pg/ml.

Discussion

Subjective and objective EDS are common in PD. Its main determinants include motor complications such as wearing-off symptoms, the dosage of antiparkinsonian drugs and sleep-disordered breathing. Severe, 'narcolepsy-like' EDS can be observed in PD even in the absence of SOREM and a detectable CSF hypocretin-1 deficit. However, PD patients tended to overestimate their sleepiness, as there were more patients (n = 5) with subjective sleepiness (ESS >10) and normal results in the objective test (normal MSL in MSLT), and only 1 patient with objective sleepiness (shortened MSL <5 min) and a normal ESS score.

Frequency and Characteristics of EDS in PD

Subjective (ESS >10 in 57%) and objective EDS (MSL in MSLT <5 min in 37%) were common in this PD population. Similar percentages were reported in previous studies [1, 3, 4], including those with unselected PD patients. As already reported in the literature [33, 34], we did not find an association between EDS and age. Several studies have suggested a higher frequency of EDS in male PD patients [1, 16]. In our sample, however, no gender differences were found.

An association between EDS and SOREM has been reported. Healthy subjects with multiple SOREMs were sleepier [35–37] than subjects with 1 or no SOREM. None of the 11 patients with MSL ≤5 min presented with SOREM. Because naps were terminated after 20 min (instead of allowing the patients to sleep at least 15 min after sleep onset), we do not report on the occurrence of SOREM in the rest of the patients.

Sleep-misperception was observed in 10 patients (33%), which is similar to previous reports in which sleep-state misperception in association with MSLT naps was reported in up to 38% of patients with PD and in 45% of patients with EDS [38]. In healthy subjects, sleep perception depends on sleep duration; after a 4-min nap, only 50% of healthy controls confirmed they had fallen asleep [39]. In a previous study, the patients with sleep misperception tended to underestimate their sleepiness in ESS [38]. No specific characteristics of PD with sleep misperception were found in our series.

There were also 5 patients who did not realize they fell asleep in at least 1 nap. These patients had longer mean sleep latencies on MSLT when compared to the rest of the study population. However, PD patients tended to overestimate their sleepiness, as there were more patients (n = 5) with subjective sleepiness (ESS >10) and normal results in the objective test (normal MSL in MSLT), and only 1 patient with objective sleepiness (shortened MSL <5 min) and a normal ESS score.

As already shown by others [10], ESS correlated significantly with MSL. This supports the use of ESS as a screening tool in clinical practice for EDS in PD patients.

Determinants of EDS in PD

Levodopa equivalent dose, sleep-disordered breathing, wearing-off phenomena and REM sleep amount during polysomnography were linked to EDS in our study (see below).

EDS and Neurodegeneration (PD Severity)

The neurodegenerative process itself has been implicated in the pathophysiology of EDS in PD. Longer disease duration [1, 40] and association with UPDRS III [41] and the HY stage [14, 18, 41] have been reported. In our series, patients with advanced/severe PD (HY $\geq$3) did not differ from patients with light/beginning PD (HY $<$3). However, patients with motor fluctuations – a sign of advanced PD – had significantly lower mean sleep latencies on MSLT. This may be related to the involvement, usually later in the course of PD, not only of the nigrostriatal dopaminergic system but also of extrastriatal dopaminergic and non-dopaminergic neurons in the lower brainstem and midbrain [42] involved in sleep-wake regulation [43, 44].

EDS and Treatment

We found a dose-dependent effect for both dopamine agonists and the overall levodopa equivalent dose on EDS, but not for levodopa alone. Others have similarly shown that dopamine agonists [45] and the total levodopa equivalent dose [3, 14] are associated with EDS. Additionally, patients on levodopa monotherapy had lower risk for sleep attacks than patients on dopamine agonist monotherapy or patients on a combination of levodopa and a dopamine agonist [16]. Patients with sleep episodes while driving had a higher levodopa equivalent dose than those without [46]. In 15 untreated patients with PD, ESS increased and MSL decreased significantly after initiation of levodopa treatment [9]. These findings suggest that both the use of dopamine agonists and the levodopa equivalent dose are associated with excessive daytime sleepiness.

EDS and Polysomnographic Findings

In our series, 3 polysomnographic parameters (sleep latency, AHI, sleep latency, REM-sleep amounts) were linked to EDS.

Sleep latencies (at night and during the day) are markers of sleep propensity. Patients with shorter sleep latency at night also had shorter MSL during the day (during MSLT) and higher ESS scores, as partially shown by others [3, 4].

Sleep-disordered breathing (AHI $\geq$10) was found in one third of our patients. Compared to patients without sleep-disordered breathing, this group had lower mean sleep latencies on MSLT, but similar ESS. Sleep-related breathing disorders may, therefore, contribute to EDS in PD patients, very likely without representing its main cause in most cases [5, 12]. In 2 of our patients, CPAP was attempted, but not tolerated.

EDS and CSF Hypocretin-1 Levels

CSF hypocretin-1 level was measured in 3 of our patients and was in the normal range, confirming that EDS in PD may be severe even in the absence of a detectable hypocretin deficiency [11, 23, 24].

Conclusion

Subjective and objective EDS are common in PD patients. Wearing-off symptoms, dosage of antiparkinsonian drugs and sleep-disordered breathing (but not age, gender or disease duration) are linked with EDS in PD patients. Severe, 'narcolepsy-like' EDS can be observed in PD even in the absence of SOREM and a detectable CSF hypocretin-1 deficit.

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